REMARKS

Claims 1, 2, 4, and 14-23 were pending in this application. Claims 1, 2, 4, and 18-21 have been amended, claims 17, 22, and 23 have been canceled, and new claims 24 and 25 have been added. Accordingly, upon entry of this amendment, claims 1, 2, 4, 14-16, 18-21, 24, and 25 will be pending.

Support for the claim amendments presented herein may be found throughout the specification and claims, as originally filed, and/or as previously examined. Specifically, support for the amendment to claims 1 to recite "XBP-1 knockout (XBP-1-/-) mouse embryo" and "chimeric XBP-1 knockout (XBP-1-/-) / RAG-2 knockout (RAG-2-/-) mouse" may be found, for example, fourth full paragraph of the specification, 1, page 56, last paragraph, through page 57, first paragraph of the specification and Example 2, page 63, first full paragraph of the specification. *No new matter has been added.*

Any amendments to and/or cancellation of the claims are not to be construed as acquiescence to any of the rejections set forth in the instant Office Action, and were done solely to expedite prosecution of the application. Applicants hereby reserve the right to pursue the subject matter of the claims as originally filed in this or a separate application(s).

Applicants respectfully submit that the amendments presented herein bring the claims into condition for allowance. Furthermore, Applicants submit that no additional search is required and no new issues have been raised by the amendments made herein. Moreover, in view of the amendments, cancellations, and arguments set forth herein, the number of issues for appeal have been reduced. Specifically, Applicants submit that the claim amendments and cancellations presented herein obviate the Examiner's rejections under §112, first paragraph and §112, second paragraph.

In particular, Applicants submit that the generic phrase "XBP-1 deficient mice", which embraces the specific mice and embryos, thereof recited in the phrases "XBP-1 knockout (XBP-1-/-) mouse embryo" and "chimeric XBP-1 knockout (XBP-1-/-) / RAG-2 knockout (RAG-2-/-) mouse", has already been searched and, thus, the phrases "XBP-1 knockout (XBP-1-/-) mouse embryo" and "chimeric XBP-1 knockout (XBP-1-/-) / RAG-2 knockout (RAG-2-/-) mouse" will not require further search. Therefore, the claim amendments, cancellations, and new claims

presented herein are permissible under 37 C.F.R. §1.116 as reducing the number of issues for appeal, and Applicants respectfully request that the present Amendment be entered.

Rejection of Claims 1, 2, 4, and 14-23 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1, 2, 4, 14-23 under 35 U.S.C. §112, first paragraph because, according to the Examiner, "[t]he claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." In particular, the Examiner is of the opinion that "the specification, while being enabling for making and using XBP-1 knockout mouse embryo or chimeric mice that is XBP-1 deficient/RAG2 deficient, does not reasonably provide enablement for making and using XBP-1 knockout mice or XBP-1 conditional knockout mice."

Applicants respectfully traverse the foregoing rejection for the reasons of record and submit that, based on the teachings in Applicants' specification and the knowledge generally available in the art at the time of the invention, one of ordinary skill in the art would be able to perform the claimed screening assays using no more than routine experimentation.

In particular, Applicants submit that the teachings in the specification provide sufficient guidance to allow one of ordinary skill in the art to generate XBP-1 deficient mice and isolate cell from such animals for use in the claimed methods. Specifically, Applicants specification provides teachings regarding the production of a non-human XBP-1-deficient mouse by homologous recombination or blastocyst complementation, techniques conventionally known in the art at the time of filing. In particular, at page 23, first full paragraph, through page 24, Applicants' specification teaches that

> [n]on-human animals deficient in a particular gene product typically are created by homologous recombination. Briefly, a vector is prepared which contains at least a portion of the XBP-1 gene into which a deletion, addition or substitution has been introduced to thereby alter, e.g, functionally disrupt, the endogenous XBP-1 gene. The XBP-1 gene preferably is a mouse XBP-1 gene. For example, a mouse XBP-1 gene can be isolated from a mouse genomic DNA library using the mouse XBP-1 cDNA as a probe. The mouse XBP-1 gene then can be used to construct a homologous recombination vector suitable for altering an endogenous XBP-1 gene in the mouse genome. In a preferred embodiment, the vector

> is designed such that, upon homologous recombination, the endogenous XBP-1 gene is functionally disrupted (i.e., no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous XBP-1 gene is mutated or otherwise altered but still encodes functional protein (e.g., the upstream regulatory region can be altered to thereby alter the expression of the endogenous XBP-1 protein). In the homologous recombination vector, the altered portion of the XBP-1 gene is flanked at its 5' and 3' ends by additional nucleic acid of the XBP-1 gene to allow for homologous recombination to occur between the exogenous XBP-1 gene carried by the vector and an endogenous XBP-1 gene in an embryonic stem cell. The additional flanking XBP-1 nucleic acid is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see e.g., Thomas, K.R. and Capecchi, M. R. (1987) Cell 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced XBP-1 gene has homologously recombined with the endogenous XBP-1 gene are selected (see e.g., Li, E. et al (1992) Cell 69:915). The selected cells are then injected into a blastocyst of an animal (e.g., a mouse) to form aggregation chimeras (see e.g., Bradley, A. in Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, EJ. Robertson, ed. (ERL, Oxford, 1987) pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, A. (1991) Current Opinion in Biotechnology 2:823-829 and in PCT International Publication Nos.: WO 90/11354 by Le Mouellec et al.; WO 91/01140 by Smithies et al; WO 92/0968 by Zijlstra et al.; and WO 93/04169 by Berns et al.

Applicants' specification further teaches at page 22, first paragraph,

> a "conditional knock-out" system, in which the XBP-1 gene is rendered non-functional in a conditional manner, can be used to create XBP-1 deficient hepatocytes (or hepatocyte precursors) for use in screening assays. For example, a tetracycline-regulated system for conditional disruption of a gene as described in WO 94/29442 and U.S. Patent No. 5,650,298 can be used to create hepatocytes (or hepatocyte precursors), or XBP-1 deficient animals from which hepatocytes (or hepatocyte precursors) can be isolated, that can be rendered XBP-1 deficient in a controlled manner through modulation of the tetracycline concentration

> in contact with the cells. For assays relating to plasma cell differentiation or T cell subset activity, a similar conditional disruption approach can be used or, alternatively, the RAG-2 deficient blastocyst complementation system can be used to generate mice with lymphoid organs that arise from embryonic stem cells with homozygous mutations of the XBP-1 gene (see Example 2). XBP-1 deficient lymphoid cells (e.g., thymic, splenic and/or lymph node cells) or purified XBP-1 deficient B cells or T cells from such animals can be used in screening assays.

Moreover, as acknowledged by the Examiner, Applicants have provided working Examples teaching the production of mice deficient in XBP-1. Specifically, Example 1 teaches the generation of XBP-1 knock-out mice by disruption of the endogenous XBP-1 gene in embryonic stem cells (see page 56, last paragraph, through page 57, first paragraph). Example 2, teaches the generation of a conditional knock-out allele of the XBP-1 gene and the production of chimeric mice using Rag-2 deficient blastocysts.

Thus, Applicants respectfully submit that based on the teachings and guidance provided by Applicants in the specification in combination with the general knowledge available to one of skill in the art at the time the application was filed, one of skill in the art would be able to make and use an XBP-1 deficient mouse and perform the claimed screening assays using no more than routine experimentation.

Nonetheless, in the interest of expediting prosecution of the application and in no way acquiescing to the validity of the Examiner's rejection, claim 1, and claims dependent therefrom, have been amended such that they are now directed to screening methods using a "***XBP-1 knockout (XBP-1-/-) mouse embryo***" and new claims 24 and 25, and claims dependent therefrom are directed to screening methods using a "***chimeric XBP-1 knockout (XBP-1-/-) / RAG-2 knockout (RAG-2-/-) mouse***", thus, rendering the Examiner's rejection moot.

Rejection of Claims 17-19 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 17-19 under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner is of the opinion that there is insufficient antecedent basis for the recitation of the limitation 'B cell activity'."

Applicants respectfully submit that the amendments to claims 18-19 and cancellation of claim 17 has rendered the foregoing rejection moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of this 35 U.S.C. §112, second paragraph rejection of claims 17-19.

Claim Objections

The Examiner has objected to claim 21 because "of the word IL1-5."

Applicants respectfully submit that correction of this typographical error such that claim 21 recites "IL-5" renders the foregoing objection moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of this objection to claim 21.

Double Patenting

The Examiner has maintained the provisional rejection of claims 1-5 under the judicially created doctrine of obviousness-type double patenting as being "unpatentable over claim 28 of U.S. Application No. 10/655,620." The Examiner states that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scopes."

Applicants respectfully reiterate that upon an indication of allowable subject matter in this or U.S. Application No. 10/655,620, Applicants will consider filing a terminal disclaimer, if appropriate.

SUMMARY

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

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Respectfully submitted,

By _____

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